VICH International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

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Guidance for Industry

Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: Carcinogenicity Testing VICH GL28

DRAFT GUIDANCE

This document is being distributed for comment purposes only

This draft guidance is to ensure that the assessment of carcinogenic potential is appropriate to human exposure through residues of veterinary drugs in food.

Comments and suggestions regarding this document should be submitted to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. Submit electronic comments to http://www.fda.gov/dockets/ecomments. All comments should be identified with the Docket No. 01D-0357.

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VICH International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

VICH GL28 (SAFETY: CARCINOGENITICY)
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For consultation at Step 4 - Draft 1

STUDIES TO EVALUATE THE SAFETY OF RESIDUES OF VETERINARY DRUGS IN HUMAN FOOD: CARCINOGENICITY TESTING

Recommended for Consultation
at Step 4 of the VICH Process
on 28 June 2001
by the VICH Steering Committee

THIS GUIDANCE HAS BEEN DEVELOPED BY THE APPROPRIATE VICH EXPERT WORKING GROUP AND IS SUBJECT TO CONSULTATION BY THE PARTIES, IN ACCORDANCE WITH THE VICH PROCESS. AT STEP 7 OF THE PROCESS THE FINAL DRAFT WILL BE RECOMMENDED FOR ADOPTION TO THE REGULATORY BODIES OF THE EUROPEAN UNION, JAPAN AND USA.

Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: Carcinogenicity Testing

This guidance represents the Agency's current thinking on carcinogenicity testing to evaluate the safety of residues of veterinary drugs in human food. It does not create or confer any rights for or on any person and does not operate to bind the FDA or public. An alternative approach may be used if such approach satisfies the requirements of applicable statutes and regulations.

1. Introduction

1.1 Objective of the Guidance

In order to establish the safety of veterinary drug residues in human food, a number of toxicological evaluations are recommended including the assessment of potential to induce neoplasia. The objective of this guidance is to help ensure that the assessment of carcinogenic potential is appropriate to human exposure through residues of veterinary drugs in food.

1.2 Background

The assessment of carcinogenic potential has been identified as one of the key areas to be considered in the evaluation of the safety of residues of veterinary drugs in human food. Exposure to residues of veterinary drugs will usually occur at extremely low levels, but potentially for long periods, possibly over a lifetime. To ensure that those substances that could pose carcinogenic potential at relevant exposure levels are adequately assessed, a number of biological endpoints should be considered, including genotoxicity, metabolic fate, species differences, and cellular changes.

1.3 Scope of the guidance

This guidance sets out the data-driven decision pathway to determine the need to conduct *in vivo* carcinogenicity studies. This guidance further provides guidance on the conduct of *in vivo* carcinogenicity studies.

2. Carcinogenicity Assessment

2.1 Overall approach

The decision to undertake carcinogenicity testing should take into consideration, 1) the results of genotoxicity tests, 2) structure-activity relationships, and 3) findings in systemic toxicity tests that may be relevant to neoplasia in longer term studies. It should also take into consideration species specificity of the mechanism and any potential differences in metabolism between the test and target animal species.

2.2 Genotoxic compounds

Assessment of the genotoxic potential of a compound should take into account the totality of findings and acknowledge the intrinsic value and limitations of both the *in vitro* and *in vivo* tests.

Many carcinogens have a genotoxic mode of action and it is prudent to regard genotoxicants as potential carcinogens unless there is convincing evidence that this is not the case. Clearly negative results for genotoxicity should usually be taken as sufficient evidence of a lack of carcinogenic potential via a genotoxic mechanism.

2.3 Non-genotoxic compounds

For non-genotoxic compounds, although carcinogenic effects can occur by epigenetic mechanisms, it is widely acknowledged that high and continuous exposures are usually required to induce neoplasia. Since human exposure to residues of veterinary drugs is low, non-genotoxic compounds do not need to be routinely tested for carcinogenicity. Such tests may however be recommended if, for example, 1) the compound is a member of a chemical class of compounds known to be animal or human carcinogens, 2) available systemic toxicity studies with the compound identify potentially preneoplastic lesions or findings indicative of neoplasia, or 3) systemic toxicity studies indicate that the compound may be associated with effects known to be linked with epigenetic mechanisms of carcinogenicity that are relevant to humans.

2.4. *In vivo* carcinogenicity testing

2.4.1. Existing relevant guidance

The OECD Test Guideline 451 "Carcinogenicity Studies," established in 1981, contains traditional study protocol guidances and approaches for testing chemicals for carcinogenicity using experimental animals. OECD Test Guideline 451 serves as the basis for this testing with the modifications outlined in the following paragraphs.

2.4.2. Species selection for long-term carcinogenicity testing

Carcinogenicity bioassays consisting of a two-year rat study and an 18-month mouse study are generally recommended. With appropriate scientific justification, carcinogenicity studies may be carried out in one rodent species, preferably the rat. A positive response in either test species should be considered indicative of carcinogenic potential.

2.4.3. Number of animals and route of administration

Consistent with OECD Test Guideline 451 and common practice, a minimum of 50 rats and/or mice per dose (including concurrent controls) per sex should be appropriate for carcinogenicity testing. The route of administration for carcinogenicity testing of veterinary drug residues in human food should be oral, preferably dietary. If agent stability in the diet is a significant consideration, oral gavage may be called for. Other routes of administration should not be generally relevant for risk assessment of veterinary drugs in human food.

2.4.4. Dose selection for carcinogenicity testing

2.4.4.1. General

It is recommended that at least three dose levels, in addition to a concurrent control group, be used for typical rodent carcinogenicity studies.

2.4.4.2. High dose selection

The high dose should be set to demonstrate a minimum toxic effect without affecting survivability due to effects other than carcinogenicity. Demonstration of a toxic effect in the carcinogenicity study, without compromising survivability or physiological homeostasis, ensures that the animals were sufficiently challenged and provides confidence in the reliability of a negative outcome.

2.4.4.3. Selection of other doses

Factors to be considered in establishing these doses include linearity of pharmacokinetics, saturation of metabolic pathways, anticipated human exposure levels, pharmacodynamics in the

test species, the potential for threshold effects in the test species, available mechanistic information, and the unpredictability of the progression of toxicity observed in short-term rodent studies. One generally accepted default paradigm is to set the lowest dose at a level that does not induce significant toxicity and is not lower than 10% of the highest dose.

2.5. In-life observations and pathologic examination

In-life observations and pathological examination, consistent with OECD Test Guideline 451, should be appropriate for carcinogenicity studies of veterinary drugs. Clinical pathology (hematology, urinalysis, and clinical chemistry) is recommended as necessary or contributory to assessment of the neoplastic endpoints.

3. REFERENCE

OECD. 1981. Test Guideline 451. Carcinogenicity Studies. In: OECD Guideline for Testing of Chemicals. Paris, Organization for Economic Cooperation & Development.